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Thermal investigation on hydrated co-amorphous systems of nicotinamide and prilocaine

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ABSTRACT

It is generally recognized that water, acting as a plasticizer, increases molecular mobility, leading to a decrease of the glass transition temperature ($T_g$) in amorphous systems. However, an anti-plasticizing effect of water was recently observed on prilocaine (PRL). This effect might be used in co-amorphous systems to moderate the plasticizing effect of water. Nicotinamide (NIC) can form co-amorphous systems with PRL. In order to investigate the effect of water on these co-amorphous systems, the $T_g$'s and molecular mobility of hydrated co-amorphous NIC-PRL systems were compared with those of the respective anhydrous systems. Molecular mobility was estimated by considering the enthalpic recovery at the $T_g$ using the Kohlrausch-Williams-Watts (KWW) equation. At molar ratios of NIC above 0.2, a plasticizing effect of water on co-amorphous NIC-PRL systems was observed with increasing the NIC concentration. In contrast, at molar ratios of NIC of 0.2 and below, water had an anti-plasticizing effect on the co-amorphous NIC-PRL systems, with increased $T_g$'s and reduced mobility upon hydration.

1. Introduction

There is a continuing and increasing interest to utilize amorphous forms of active pharmaceutical ingredients, compared to the respective crystalline state, due to their dissolution enhancement and solubility improvement [1]. These advantageous properties result from the excess free energy and enhanced molecular mobility in an amorphous solid but come at the expense of physical instability [2]. To overcome stability issues, inter alia co-amorphous systems were introduced as a formulation strategy, in which a drug and a low molecular weight co-former are mixed at the molecular level to form a two-component amorphous mixture [3].

The physical instability of amorphous materials is the result of nucleation and crystal growth, both of which are related to molecular mobility and structural relaxation behavior [4]. Amorphous drugs or homogenous amorphous systems are characterized by the glass transition temperature ($T_g$), which marks the transition from the glass, in which the molecules have lower molecular mobility, to a supercooled liquid form [5-8]. Differential scanning calorimetry (DSC) is one of the most commonly used techniques to characterize both the $T_g$ and the relaxation behavior. The latter is indirectly measured by the enthalpic recovery at the $T_g$ of an aged sample [9,10]. The kinetics of relaxation are then estimated using the Kohlrausch-Williams-Watts (KWW) equation [11].

The addition of other components can modify the $T_g$ of an active pharmaceutical ingredient (API) functioning either as plasticizers or anti-plasticizers. It is accepted that water as an effective plasticizer in amorphous systems can cause changes in physical properties by leading to greater molecular mobility and lowering of the $T_g$ [12,13]. However, recent studies showed that water can also act as an anti-plasticizer that reduced the molecular mobility of prilocaine (PRL), resulting in a higher $T_g$ of hydrated PRL compared with that of anhydrous, amorphous PRL [14,15]. The nature of the anti-plasticizing effect has not been finally elucidated, but it is speculated to be due to the interaction of water with the dimer structure of PRL [14]. Using molecular sieves to confine the PRL and water together in nanometer spaces, an anti-plasticizing effect of water on PRL could still be observed, and interactions between PRL and water were thus not affected by confinement. This may indicate that small drug-water clusters are responsible for the anti-plasticizing effect of water on PRL [15]. Our previous work suggested that water also has an anti-plasticizing effect on the structurally related drug lidocaine (LID). Furthermore, an anti-plasticization effect of water has been observed for co-amorphous systems of PRL and LID [16]. These results imply that PRL or LID might be further used in other co-amorphous systems to moderate...
the plasticizing effect of water.

Nicotinamide (NIC) was chosen as the model drug in this study due to its co-formability with PRL [17]. The aim was to provide an understanding of the effect of water on co-amorphous NIC-PRL systems. Melt-quenching was used to prepare anhydrous co-amorphous NIC-PRL systems at various molar ratios, which were subsequently hydrated by addition of water. The Tg's and relaxation behavior were examined for both anhydrous and hydrated co-amorphous systems. An anti-plasticizing effect of water was claimed if the Tg's of hydrated NIC-PRL were higher and molecular mobility was lower compared to the respective anhydrous systems.

2. Materials and methods

2.1. Materials

NIC (MW = 122.12 g/mol) was purchased from Merck KGaA (Darmstadt, Germany). PRL (MW = 220.31 g/mol) was purchased from Fluorochem ltd. (Hadfield, U.K.). Water (18.2 MΩ) was freshly prepared using a Milli-Q water system from ELGA LabWater (High Wycombe, U.K.). The chemical structures of NIC and PRL are shown in Figure S1.

2.2. Methods

2.2.1. Sample preparation

Co-amorphous NIC-PRL samples were prepared by melting crystalline mixtures followed by quench-cooling in a Discovery DSC (TA instruments, New Castle, USA) at molar ratios of NIC to NIC-PRL from 0.1 to 0.8. For anhydrous samples, crystalline mixtures of PRL and NIC (approximately 8 mg) were sealed with a hermetic lid with a pinhole to enable absorbed water to evaporate during heating. For hydrated samples, a drop of water was added into the anhydrous crystalline mixtures. The evaporation of water was monitored on a microbalance until the endothermic peak at the Tg of the hydrated NIC-PRL sample was reached. For the final analysis, hermetic aluminum pans were employed for hydrated samples to avoid water evaporation.

2.2.2. Thermal analysis

Temperature modulated DSC was performed under a nitrogen gas flow of 50 mL/min. The samples were heated to 411.15 K and cooled to 203.15 K at a ballistic cooling rate (>750 K/min). Subsequently, the quench-cooled samples were reheated to predetermined temperatures (30 K above the respective Tg's of the co-amorphous samples) at a linear heating rate of 2 K/min with a sinusoidal modulation. The modulation amplitude was 0.2120 K, and the period was 40 s. The Tg was taken at the midpoint of the change in heat capacity (ΔCp). The Tg values were determined in triplicate.

Relaxation enthalpy (as recovered enthalpy) (ΔHr) was evaluated at 15 ± 1 K below the experimental Tg. A single measurement of relaxation behavior was performed for predetermined time intervals (1, 2, 4, 8, and 16 h). ΔHr was obtained from the endothermic peak at the Tg. The Tg, ΔCp, and ΔHr were determined using TRIOS software (version 5.1.1). The instrument was calibrated for temperature and heat flow using indium.

2.2.3. Theoretical considerations

2.2.3.1. Theoretical Tg based on the Gordon-Taylor equation. The Gordon-Taylor equation is commonly used to predict the Tg of ideally mixed binary co-amorphous systems [18]:

\[ T_{g12} = \frac{w_{1}T_{g1} + K w_{2}T_{g2}}{w_{1} + K w_{2}} \]

(1)

where \( T_{g12} \) is the Tg of a co-amorphous system, \( T_{g1}, T_{g2} \), \( w_{1}, w_{2} \) are the Tg's and the weight fractions of the individual components. The parameter K can be estimated according to the Simha-Boyer rule [19]:

\[ K = \frac{T_{g1} \rho_{1}}{T_{g2} \rho_{2}} \]

(2)

where \( \rho_{1} \) and \( \rho_{2} \) are the densities of the two amorphous components. The densities of crystalline drugs were used in this study (\( \rho_{\text{NIC}} = 1.400 \text{ g/cm}^3 \), \( \rho_{\text{PRL}} = 1.029 \text{ g/cm}^3 \)), as the densities of amorphous NIC and PRL cannot be determined due to fast recrystallization and low Tg's [20,21]. This approximation is deemed valid for small molecules [22].

2.2.3.2. Structural relaxation based on the KWW equation. Molecular mobility was evaluated using the KWW equation, which is based on the assumption that when heating a relaxed drug from the annealing temperature through the Tg, the recovered enthalpy can be determined from the endothermic peak at the Tg [8]. The KWW equation is expressed as follows:

\[ \varphi(t) = 1 - \frac{\Delta H}{\Delta H_{\infty}} = \exp \left[-\left(\frac{t}{\tau}\right)^{\beta}\right] \]

(3)

where \( \varphi(t) \) is the proportion of unrelaxed amorphous component at the annealing time t. \( \Delta H_{\infty} \) is the recovered enthalpy at the Tg upon annealing, \( \tau \) is the relaxation time, and \( \beta \) is a stretched exponential parameter \( 0 < \beta < 1 \), respectively. \( \tau \) and \( \beta \) are two adjustable parameters. A fitting process was carried out to determine \( \tau \) and \( \beta \) using OriginPro 2020 software (OriginLab, Northampton, MA, USA). \( \Delta H_{\infty} \) is the theoretical maximum relaxation enthalpy, and can be estimated as follows:

\[ \Delta H_{\infty} = (T_{g} - T) \times \Delta C_{p} \]
where ΔCp is heat capacity change at the Tg, and T is the annealing temperature.

3. Results and discussion

3.1. Tg of anhydrous co-amorphous NIC-PRL systems

The experimental Tg of PRL was found to be 219.4 ± 0.1 K, in good agreement with the values reported by Ruiz et al. [15]. It was not possible to determine the Tg of NIC due to the instability of amorphous NIC, as recrystallization was observed during cooling of the drug melt. A previous study, however, stated that NIC can be made fully amorphous by quenching the drug melt in liquid nitrogen, resulting in a Tg of 265.7 ± 0.2 K [23]. Due to the high crystallization tendency of amorphous NIC, it is practically impossible to determine the experimental Tg of NIC-PRL co-amorphous systems with molar ratios of NIC higher than 0.8. At molar ratios of NIC of 0.8 and below, the appearance of a single Tg, indcated the formation of homogenous co-amorphous systems of NIC-PRL. The experimental Tg were compared with the theoretical Tg based on the Gordon-Taylor equation (Fig. 1A). All the experimental Tg showed positive deviations from the theoretical Tg, indicating the presence of molecular interactions between NIC and PRL [24]. As the pKα values of NIC (pKα = 14.83) [20] and PRL (pKα = 14.24) [21] are similar, hydrogen bonding can be rationalized between the two components as no proton transfer is likely [25]. In order to give a clearer picture of the deviations between the experimental and theoretical Tg, the dependence of deviations on the ratio of NIC is illustrated in Fig. 1B. The largest deviations of Tg were observed at molar ratios of NIC of 0.6 and 0.7, indicating that NIC and PRL may have more mutual interactions at molar ratios of NIC of 0.6 and 0.7 than at the other mixing ratios.

3.2. Molecular mobility of anhydrous co-amorphous NIC-PRL systems

The enthalpic relaxation behavior of NIC-PRL as a function of aging time was used to study the molecular mobility of the amorphous form below the Tg. The glass can be converted to the equilibrium supercooled liquid through enthalpy loss during aging below the Tg. The lost enthalpy can be regained upon reheating and observed as an enthalpic recovery at the Tg [6,8,26]. Fig. 2A shows a reduction of the proportion of unrelaxed amorphous component according to the KWW equation as a function of the annealing time. The relaxation behaviors of NIC-PRL with NIC molar ratios of 0.6 and 0.7 were similar over the observed annealing time. In order to quantify the relaxation behavior, the experimental data were fitted with the KWW equation, and the parameters τ and β are summarized in Table S1. While τ can usually be applied for direct comparison in single component amorphous systems, the situation is more complex for multi-component systems. A comparison of

\[ t_{1/2} = (\ln 2)^{1/\beta} \tau \]  

(5)

The t1/2 values of anhydrous NIC-PRL with varying molar ratios of NIC are shown in Fig. 2B. A maximum was observed for NIC-PRL (0.6) and NIC-PRL (0.7) as those systems relaxed considerably slower than the other anhydrous co-amorphous NIC-PRL systems. The obviously restricted molecular mobility was in good agreement with the observed maximum in the deviations of the Tg of NIC-PRL (0.6) and NIC-PRL (0.7) observed earlier in Fig. 1B.

3.3. Comparison of the Tg of hydrated co-amorphous NIC-PRL systems

It is generally known that the Tg of an amorphous sample can be reduced by the addition of water, due to the ability of water to form hydrogen bonds with molecules in the amorphous phase [30]. The effect of varying amounts of water on the Tg of NIC-PRL systems is shown in Fig. 3. The DSC thermograms of anhydrous and hydrated NIC-PRL
systems are shown in Figure S2.

In anhydrous co-amorphous NIC-PRL systems, a linear relationship \( R^2 = 0.995 \) was observed between the \( T_g \) and the molar ratios of NIC. In the presence of water, also a linear relationship was observed \( R^2 = 0.977 \). This indicated an even distribution of water between NIC and PRL. However, the slope of the \( T_g \) over the molar ratio of NIC was lower for hydrated systems compared with anhydrous systems. Previous work showed that the \( T_g \) of hydrated PRL can be increased by 4.2 K compared with the \( T_g \) of PRL, at a maximum hydration of \( X_{H2O} = 50\% \) [14,16]. Thus, a hydration of \( X_{H2O} = 50\% \) was chosen to investigate the \( T_g \) of hydrated NIC-PRL in order to maximize the anti-plasticizing effect of water on PRL. It was found that the \( T_g \) of hydrated NIC-PRL with molar ratios of NIC of 0.1 and 0.2 increased by 2.1 \( \pm \) 0.5 K and 0.6 \( \pm \) 0.2 K compared with the respective \( T_g \) of anhydrous NIC-PRL. The \( T_g \) of NIC-PRL (0.1) and NIC-PRL (0.2) were significantly increased upon hydration (student t-test, \( P < 0.05 \)). This again shows an anti-plasticizing effect of water on the \( T_g \) of these NIC-PRL systems. In contrast, at molar ratios of NIC above 0.2, the \( T_g \) of hydrated NIC-PRL were lower than the \( T_g \) of anhydrous NIC-PRL, confirming a plasticizing effect of water.

In order to further investigate the influence of water on the molecular interactions between NIC and PRL, the \( T_g \) were compared with the theoretical \( T_g \) based on the Gordon-Taylor equation with the two approaches. For the first approach, the theoretical \( T_g \) of hydrated NIC-PRL were calculated regarding “anhydrous NIC-PRL” as a single component in equation (1), and water as the second component. For the second approach, the theoretical \( T_g \) of hydrated NIC-PRL were calculated without considerations of additional interactions between “hydrated NIC” and “hydrated PRL”. Based on the above findings shown in Fig. 3, it was assumed that water distributed evenly between NIC and PRL in hydrated NIC-PRL. The \( T_g \) of hydrated NIC and the \( T_g \) of hydrated PRL with the same hydration level were treated as two components in equation (1). The \( T_g \) of hydrated PRL and hydrated NIC with various water concentrations \( X_{H2O} \) are summarized in Table S2.

As shown in Fig. 4, there was a general tendency that the experimental \( T_g \) of NIC-PRL decreased with increasing water concentration, especially at high NIC ratios, presumably due to a plasticizing effect of water on NIC-PRL. For Fig. 4A the theoretical \( T_g \) of hydrated NIC-PRL were calculated by regarding water as one component which can only plasticize co-amorphous NIC-PRL systems. The experimental \( T_g \) of NIC-PRL (0.2) and NIC-PRL (0.5) were larger than the theoretical \( T_g \), indicating that the assumption of water always being a plasticizer of the co-amorphous system is not fulfilled. However, at high NIC ratios, the plasticizing effect of water becomes more dominant as can be seen in the decrease in the differences between the experimental \( T_g \) and the theoretical \( T_g \).

As the first model could not completely explain the experimental observations, especially at low NIC ratios, another model was used. In Fig. 4B, the theoretical \( T_g \) of NIC-PRL upon hydration were calculated by regarding water as an anti-plasticizer on PRL and a plasticizer on NIC. For NIC-PRL (0.2), the difference between the experimental and theoretical \( T_g \) remained similar with increasing water concentration, indicating that the theoretical \( T_g \) based on the second model could better fit the experimental \( T_g \) compared with the first. Thus the second model is used to explain the influence of water on the original intermolecular interactions between NIC and PRL. The similar trend of the experimental \( T_g \) and the theoretical \( T_g \) of NIC-PRL (0.2) upon hydration suggests that water interacts with NIC and PRL individually but the interactions between NIC and PRL are still maintained. However, for NIC-PRL (0.5), the difference between the experimental and theoretical \( T_g \) decreased with increasing water concentration. The original interactions between NIC and PRL might thus be disrupted by water. Upon a further increase in NIC concentration to NIC-PRL (0.8), the differences between the theoretical and experimental \( T_g \) decreased even further. The experimental \( T_g \) even became lower than the theoretical \( T_g \) above \( X_{H2O} = 40\% \).

In summary, the decrease in the difference of the \( T_g \) upon hydration (observed from Fig. 4B) was larger at high NIC ratios, associated with an obvious decrease in the experimental \( T_g \) in the presence of water, probably as the consequence of a plasticizing effect of water on NIC-PRL.
3.4. Molecular mobility of hydrated co-amorphous NIC-PRL systems

Fig. 5. Comparison of $\tau_{1/2}$ values between anhydrous co-amorphous NIC-PRL and hydrated co-amorphous NIC-PRL systems with $X_{H2O} = 50\%$ systems.

The $\tau_{1/2}$ values of anhydrous and hydrated systems were used to evaluate the molecular mobility in the systems (Fig. 5). At molar ratios of NIC of 0.1 and 0.2, increased $\tau_{1/2}$ values of hydrated NIC-PRL were seen, compared with those of the respective anhydrous NIC-PRL systems, indicating a decrease in molecular mobility upon hydration. In contrast, at molar ratios of NIC above 0.2, decreased $\tau_{1/2}$ values of hydrated NIC-PRL were seen, compared with those of the respective anhydrous NIC-PRL systems. This means that the molecular mobility of hydrated NIC-PRL increased compared with that of the respective anhydrous NIC-PRL systems.

At molar ratios of 0.6 and 0.7, extremely high $\tau_{1/2}$ values were observed for the anhydrous NIC-PRL systems, indicating a rather restricted molecular mobility. In the presence of water, these $\tau_{1/2}$ values decreased notably, reaching a higher level of mobility, comparable with the other hydrated systems. The fitting results for the KWW equation of hydrated NIC-PRL are summarized in Table S3. Therefore, the effect of water on the molecular mobility of NIC-PRL was also associated with NIC-PRL ratios. With the addition of water, an increase in $\tau_{1/2}$ values (decrease of molecular mobility) can only be maintained at low NIC proportions.

4. Conclusions

In this study, the $T_g$ and molecular mobility of hydrated co-amorphous NIC-PRL systems were compared with those of anhydrous NIC-PRL. At molar ratios of NIC of 0.2 and below, addition of water increased the $T_g$ and decreased molecular mobility, indicating an anti-plasticizing effect of water on these co-amorphous NIC-PRL systems. At molar ratios of NIC above 0.2, a plasticizing effect of water was observed with increasing NIC concentration. In conclusion, this study shows that water can have both a plasticizing as well as an anti-plasticizing effect on co-amorphous NIC-PRL systems, depending on the NIC-PRL ratio.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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